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ON THE MANNER OF ACTION OF THE ANTIMICROBIAN ACTIVITY OF CHLORPROMAZINE AND ON CERTAIN ELECTRONIC ASPECTS OF THE ANTAGONISTIC ACTION OF ADENOSINE-5-TRIPHOSPHATE

/Following is a translation of an article by
Michel Faguet and Mme Andree Goudot, of the
Bacteriophage Service of the Pasteur Insti-
tute, presented at the 17 December 1962 meet-
ing of the French Academy of Sciences and
published in the French-language periodical
Comptes rendus de l'Academie des Sciences
(Reports of the Academy of Sciences). Vol 256,
1963, pages 531-533, under the subject head-
ing of Bacteriology./

The antimicrobian activity of chlorproma-
zine on staphylococcus was studied in vitro, as
the antagonistic action of adenosine-5-triphos-
phate. An electronic interpretation is given.

We studied the antimicrobian activity of chlorproma-
zine (4560 RP) with regard to gram-positive aerobic germs
(staphylococcus) and gram-negative germs (colibacilli),
which has already been the subject of several articles (J.
L. Bourdon, Ann. Inst. Pasteur, 101, 1961, pp 876-886).
We used a certain number of strains and a subsequent arti-
cle will give the detailed results. We observed that chlor-
promazine had a considerable antimicrobian action, in vitro,
with respect to such gram-positive germs as staphylococcus,
and much weaker with regard to such gram-negative germs as
colibacillus.

In this report we shall give only our results concern-
ing staphylococcus (strain Tw).

We used the technique of continuous recordings of the
curves of microbian growth by means of the "MECI" electronic

microbiophotometer (M. Faguet, Ann. Inst. Pasteur, 97, 1959, pp 177-187). The culture medium used was water with 3% peptone and 0.3% glucose. The pH was adjusted to 7.4.

Results. A 0.14×10^{-3} mol concentration of chlorpromazine is necessary to make the speed of multiplication v (control culture) pass to v/3 (speed of multiplication = number of divisions per hour), in a given area of the exponential phase. In order to obtain the same result with penicillin, it was necessary to use it in a 10^{-7} mol concentration.

Therefore, chlorpromazine displays, in vitro, a considerable antimicrobian action with regard to staphylococcus. It is known, moreover, that it causes considerable alterations of the bacterial wall in this germ and that it has no antibacterial action in vivo (Bourdon, loc. cit.).

In addition, we established the antagonistic action of ATP-K$^+$ with respect to the antistaphylococcic activity of chlorpromazine (Fig. 1).

The fact that chlorpromazine inhibits the growth of a culture of staphylococcus in vitro, regardless of whether it has no action in vivo, or, on the other hand, of whether the growth of the staphylococcus, stopped by it, starts up again in the presence of ATP-K$^+$, suggests that its ineffectiveness in vivo is perhaps due to the presence of such compounds.

It is, therefore, interesting to become familiar with the action mechanism of ATP-K$^+$ on chlorpromazine. The metallic cation, in the presence of ATP and of chlorpromazine, forms a complex in which it is jointed to two O atoms of the terminal phosphate of the ATP, the nitrogen of the aliphatic component (a free pair on N) by a covalent bond and Cl of the phenothiazine component. This will undoubtedly have the effect of putting the aliphatic component in the plane of the cyclic component.
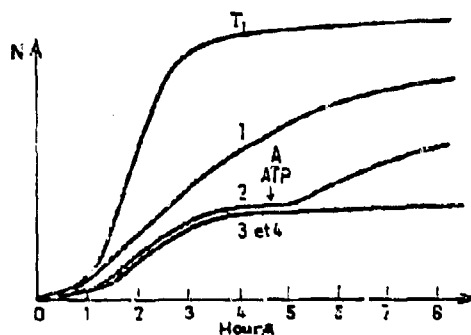
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Fig. 1. Growth curves of a staphylococcus (strain Tw).

/Legend:/ T 1 = control curve; 1 = growth curve in the presence of chlorpromazine (0.14 X 10^{-3} mol) and ATP-K^{+} (10^{-4} mol); 2 = growth curve in the presence of chlorpromazine (0.14 X 10^{-3} mol); arrow A indicates the addition of ATP-K^{+} (10^{-4} mol), followed by renewal of growth; 3 and 4 = control curves, only chlorpromazine (0.14 X 10^{-3} mol).

1. Calculation of the Energy Levels of the Mobile Electrons. Occupied levels: 3.515, 3.402, 2.408, 2.193, 1.890, 1.779, 1.664, 1.584, 1.572. Lowest free level: 1.403.

The results are different from the ones obtained (B. Pullman & l A. Pullman, Results of Quantum Mechanical Calculation of the Electronic Structure of Biochemicals, 1961, 2) for phenothiazine, for we introduced the aliphatic component and K^{+} into the calculations.

2. Charges (Fig. 2). The CH_2 (+0.54) group that binds the aliphatic component to N of the plane component is strongly positive and is located between two appreciably neutral atoms: N (+0.07) and CH_2 (+0.04).
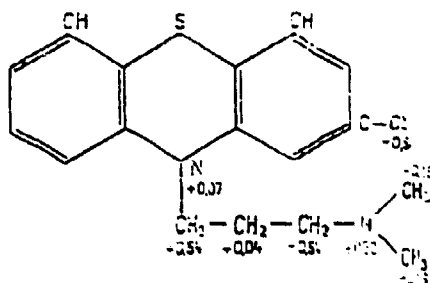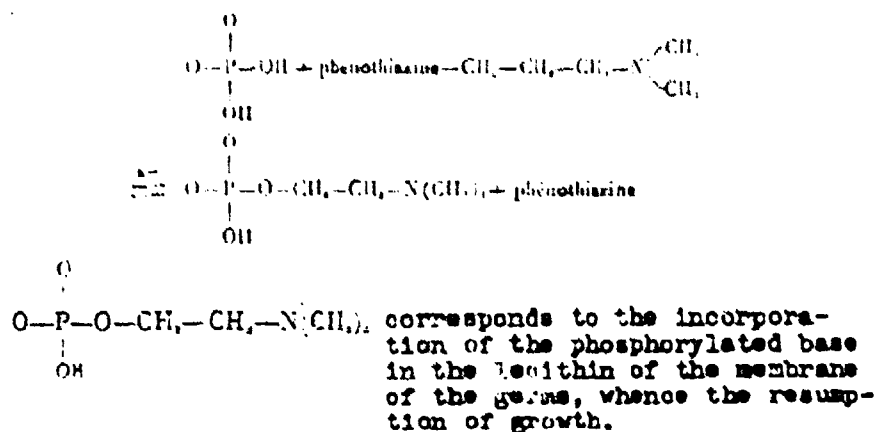
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Figure 2. Charges

Therefore, there are only labile bonds and more especially with the N of the cyclic component. The chlorpromazine molecule, therefore, has a great tendency to lose its aliphatic component and to give phenothiazine, since the CH_2 (+0.54) group of the aliphatic component is joined to the terminal phosphate group of the ATP.

To summarize, it is known that chlorpromazine acts especially by altering the microbian wall (Bourdon, loc. cit.) and that, on the other hand, it inhibits, in vivo, the incorporation of P_{32} into the lecithins (K. Bloch, Lipide Metabolism, New York: J. Wiley, 1960). The results of our experiments show that in the presence of ATP-K^+ the growth of the bacterial culture resumes. The results obtained by calculation seem able to explain the experimental results. In fact, if the distribution of the charges in the presence of ATP-K^+ is considered, it is evident that the following reaction occurs:

$O-P-O-CH_2-CH_2-N(CH_3)_2$ corresponds to the incorporation of the phosphorylated base in the lecithin of the membrane of the germs, whence the resumption of growth.

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- 4 -